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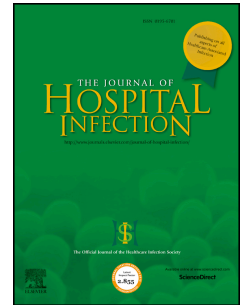
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ICU-acquired bacteraemia and ICU mortality and discharge: addressing time-varying confounding using appropriate methodology

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Running head: ICU-acquired bacteraemia outcomes

Abstract

Background: Studies often ignore time-varying confounding or use inappropriate methodology to adjust for time-varying confounding.

Aim: We estimated the effect of ICU-acquired bacteraemia on ICU mortality and discharge using appropriate methodology.

Methods: Marginal structural models with inverse probability weighting were used to estimate the ICU mortality and discharge associated with ICU-acquired bacteraemia among patients who stayed more than 2 days at the general ICU of a London teaching hospital and remained bacteraemia-free during those first two days. For comparison, the same associations were evaluated with 1) a conventional Cox model, adjusting for only baseline confounders and 2) a Cox model adjusting for baseline and time-varying confounders.

Findings: Using the marginal structural model with inverse probability weighting, bacteraemia was associated with an increase in ICU mortality (cause-specific hazard ratio [CSHR] 1.29, 95% CI 1.02-1.63) and a decrease in discharge (CSHR 0.52, 95% CI 0.45-0.60). By 60 days, among patients still in the ICU after 2 days and without prior bacteraemia, 8.0% of ICU-deaths could be prevented by preventing all ICU-acquired bacteraemia cases. The conventional Cox model adjusting for time-varying confounders gave substantially different results: CSHR 1.08 (95% CI 0.88-1.32) for ICU mortality and CSHR 0.68 (95% CI 0.60-0.77) for discharge.

Conclusion: In our study, even after adjusting for the timing of acquiring bacteraemia and time-varying confounding using inverse probability weighting for marginal structural models, ICU-acquired bacteraemia was associated with a decreased daily ICU discharge risk and an increased risk of ICU mortality.

Keywords: burden; intensive care units; bacteraemia; inverse probability weighting; bias

Introduction

Nosocomial bacteraemia is a potentially life-threatening condition that is estimated to affect 240,000 people in Europe annually.¹ Patients in intensive-care units (ICUs) are at particularly high risk of acquiring bacteraemia due to frequent invasive healthcare interventions.²

Estimating the health impact and cost per case is essential to enable health economic evaluations comparing different interventions, determine cost-effective options and justified level of investment in control. There are a large number of studies that have estimated the potential impact of ICU-acquired bacteraemia on mortality and discharge.²⁻¹² Nevertheless, the effect of ICU-acquired bacteraemia on mortality and length of stay is still uncertain.¹¹ Part of the variation in estimates can be explained by differences in case-mix, quality of care and antimicrobial resistance rates. However, there are also a number of methodological issues, which can impact estimates and are often overlooked. The fact that ICU-acquired infections have a time-dependent nature has often been ignored. For instance, comparisons of ever-infected versus never-infected patients ignore that patients need to survive long enough in order to acquire infection, thus giving an apparent survival benefit to the ever-infected patients.¹³ Time-dependent exposures can be modelled using time-dynamic models, such as time-dependent survival or multi-state models.¹³

However, even when using time-dependent survival or multi-state models, assessment of the infection effect may be biased due to confounding by severity of illness. Adjusting for all confounders measured at the time of ICU admission may not be sufficient as patients who develop bacteraemia may deteriorate more prior to bacteraemia than patients who stay bacteraemia-free. The aforementioned techniques for time-dependent exposures fail to correctly adjust for such time-dependent confounding.^{14,15} They eliminate the effect of infection that is mediated through later severity of illness, thus potentially wiping out all of the infection's effect. They moreover induce a so-called collider-stratification bias which may induce artificial correlations between infection and mortality, even in the absence of an effect (Appendix 1).¹⁶ To accommodate this, we will make use of inverse probability weighted methods for marginal structural models.¹⁷

A further factor that may complicate interpretation occurs due to the fact that patients who stay longer in the ICU are at greater cumulative risk of death. For example, even if bacteraemia does not influence the daily risk of dying, one may still observe an apparent increase in cumulative mortality if infection increases length of stay. This issue can be solved by estimating the effect on the cumulative incidence of ICU death.^{18,19}

Aforementioned methodological challenges are rarely addressed simultaneously in published studies.³ We will add to the literature by simultaneously controlling for all 3 factors that complicate analysis: 1) the time-varying nature of the exposure; 2) potential time-varying confounding; 3) the presence of competing risks. We evaluate the effect of ICU-acquired bacteraemia on mortality and discharge using IPW under marginal structural models and

compare our results with estimates obtained using traditional regression methodology that ignores complicating factors.

The UK government recently published its ambition to reduce the incidence of healthcare associated Gram-negative bacteraemia by 50% by 2020.²⁰ It is important to quantify the health and economic burden of Gram-negatives to estimate justified levels of investment in their control, allowing cost-effectiveness evaluations of local and national interventions. Hence, we also evaluated the effect of bacteraemia involving Gram-negatives.

Methods

Electronic clinical records of all patients admitted to two general ICU wards at Guy's and St Thomas' hospitals, London between 2002 and 2006 were obtained.^{12,21}

We included all patients with an ICU length of stay of more than 2 days. From this cohort, we excluded patients with bacteraemia occurring during the first 2 days in the ICU as these were assumed not to be ICU-acquired.²⁻¹²

The following variables were recorded at ICU admission: age, gender, type of admission (surgical or medical) and ICU ward. The Acute Physiology and Chronic Health Evaluation (APACHE) II score, administration of antibiotics, mechanical ventilation, central lines and renal replacement therapy were recorded on a daily basis during the entire ICU stay. All these variables were considered potential confounders based on clinical considerations and the literature.

Marginal structural model with IPW

Cause-specific hazard ratios (CSHRs) for ICU mortality and discharge were obtained using marginal structural Cox regression models, fitted using IPW to adequately take into account that the history of severity of illness may be different between patients who do and do not acquire bacteraemia. To adjust for confounders, a pseudo-population was constructed in which there was no longer confounding by the considered time-dependent variables. This was achieved by reweighting patients in the risk set (those who were still present in the ICU and were bacteraemia-free) on each day.¹⁷ Hence, by giving more weight to patients that do acquire bacteraemia on a specific day despite being unlikely to acquire bacteraemia given their history of severity of illness and vice versa, an artificial population is created in which the measured confounders (severity of illness) are independent of bacteraemia. The conditional probabilities used in the construction of the weights were set to 1 from the time of bacteraemia and onwards, and were otherwise estimated based on a pooled logistic regression model for the probability of acquiring bacteraemia in the ICU (Appendix 2).

The obtained probabilities were used to generate daily patient-specific weights. When using these weights, the analysis can become heavily dependent on a single or few individuals who

acquire bacteraemia despite having a very low predicted probability to acquire bacteraemia or vice versa, thereby resulting in very large standard errors. To overcome this problem, stabilized weights multiplying the generated weights by the product of the conditional probability of the observed infection status before that day, as obtained from a similar pooled logistic regression model that included only baseline covariates; these same covariates were included in the marginal structural model.²²

The marginal structural models were fitted using weighted Cox regression with robust standard errors. To evaluate the effect of ICU-acquired bacteraemia we included a time-varying binary indicator whether or not bacteraemia was acquired at or before the considered time, as well as the baseline covariates used for stabilization of the weights.²¹ The latter is necessary, because the stabilized weights create a pseudo-population in which there may still be confounding by the variables used for stabilization.²²

In the marginal structural model for ICU death (ICU discharge), the competing event ICU discharge (ICU death) was handled as a censoring event; resulting in CSHRs. The two separate cause-specific models for ICU discharge and ICU death were subsequently combined to evaluate, for each patient at each time, what is the cumulative incidence of ICU death in the absence of bacteraemia (R code in Appendix 3). By comparing this cumulative incidence with the observed incidence the number of ICU deaths that could be prevented was estimated. Our approach is different from multi-state approaches that ignore (time-dependent) confounding,²³ and therefore less biased when such confounding is present.

Although there were no missing values at baseline, in 3.8% of the following days missing values for the APACHE II score were imputed using the last observation carried forward.

All models were built using R version 3.2.1 (packages “ipw”, “splines”, “survival”).²⁴

Comparison with conventional Cox models

In subsequent analyses we made a comparison with two commonly applied, but potentially biased, approaches: i) a Cox model ignoring potential confounding by risk-factors that change over the course of the ICU stay, thus only adjusting for base-line confounders; and ii) a Cox model regressing on baseline and time-varying factors (Appendix 4).

Comparison of Gram negative and Gram positive bacteraemia.

We also evaluated the effect of bacteraemia involving Gram-negatives. To obtain such estimates, without having to condition on a time-varying factor that is measured after the start of follow-up, we jointly modelled the probability of bacteraemia and the probability the bacteraemia involved Gram-negatives.

To obtain the inverse probability weights for this analysis, the weights previously estimated for any bacteraemia were multiplied, from the time of acquiring bacteraemia onwards, by the stabilized inverse conditional probability that the bacteraemia involved Gram-negative bacteria, given the time-varying confounders on the previous day (Appendix 2).

The CSHR for ICU mortality and discharge were subsequently obtained using marginal structural Cox regression models. Compared to the analysis modelling ‘any bacteraemia’, an additional interaction between the indicator for bacteraemia and a binary indicator for the type of pathogen involved (Gram-negative set to 1) was incorporated. To obtain the effect of Gram-negative or Gram-positive bacteraemia these parameter estimates were combined and confidence intervals were calculated using the Delta method.

To further investigate whether potential differences between bacteraemia caused by Gram-negative or Gram-positive bacteria would be likely due to the inclusion of contaminated blood samples, particularly relevant for coagulase negative staphylococci,³ we further stratified the analyses for Gram-positive bacteria into three groups: *Staphylococcus aureus*, coagulase negative staphylococci (CNS) and other Gram-positives.

Results

Between 2002 and 2006, 2,914 patients were admitted to either ICU, contributing 3,159 ICU admissions. In 21.2% of admissions (n=671), a first blood culture positive for any bacteria was obtained from the patient more than 2 days after ICU admission. Of those ICU-acquired bacteraemia cases 218 (32.5%) involved Gram-negative bacteria, while 493 (73.5%) involved Gram-positive bacteria.

The main isolated Gram-negative bacteria were *Pseudomonas* spp. (n=68), *Escherichia coli* (n=43), *Enterobacter* spp. (n=41), *Klebsiella* spp. (n=26) and *Proteus* spp. (n=17). Isolated Gram-positive bacteria were mainly coagulase negative staphylococci (n=370), *S. aureus* (n=69) and *Enterococcus* spp. (n=52). Median time from ICU admission to bacteraemia onset was 8 days (25th-75th percentile, 6-13).

Baseline patient characteristics are shown in Table I. Patients acquiring bacteraemia were more frequently male and had a slightly higher APACHE II score at admission.

Marginal structural model with IPW

To adequately address time-varying confounding, we used marginal structural models fitted using IPW. ICU-acquired bacteraemia was associated with the daily risk of ICU mortality (CSHR 1.29; 95% CI 1.02-1.63) (Table II). More detailed descriptions of the models used for each component of the analysis are provided in Appendix 1.

ICU-acquired bacteraemia was associated with a lower daily risk of ICU discharge (CSHR 0.54; 95% CI 0.47-0.62).

The inverse probability weights used in these marginal structural models had a median and mean of 0.99 and 1.01, an interquartile range and standard deviation of 0.14 and 0.31 (min 0.26, max 4.49). These values raise no concern that our results might be negatively affected by extreme weights.²⁵

The observed cumulative incidence of ICU death in the patient cohort and the expected cumulative incidence of ICU death if all ICU-acquired bacteraemia episodes would be prevented are shown in Figure 1. This figure indicates that by 60 days, among patients still in the ICU after 2 days and without prior bacteraemia, 8% of ICU-deaths could be prevented by preventing all ICU-acquired bacteraemia cases.

Comparison with more conventional Cox models

Using conventional Cox regression, ICU-acquired bacteraemia was associated with ICU mortality (CSHR 1.28; 95% CI, 1.04-1.57) and discharge (CSHR 0.51; 95% CI, 0.45-0.58) (Table II), suggesting that bacteraemia is associated with an increase in cumulative mortality not only because of a higher risk of death, but also because of longer lengths of stay.

Conventional model with adjustment for time-dependent confounders

When adjusting for time-dependent confounders using a conventional Cox model, the hazard ratio for ICU mortality was close to one (CSHR 1.08; 95% CI 0.88-1.32). Similarly, the hazard ratio for ICU discharge became weaker (CSHR 0.68; 95% CI 0.60-0.77) compared to the marginal structural model fitted using IPW.

Comparison of Gram-negative and Gram-positive bacteraemia

Gram-negative bacteraemia appeared to have a stronger effect on ICU mortality than bacteraemia involving only Gram-positive bacteria (CSHR 1.66; 95% CI 1.21-2.28 versus CSHR 1.15; 95% CI 0.84-1.58). Similarly, the association with daily ICU discharge rate was slightly stronger for ICU-acquired Gram-negative bacteraemia (CSHR 0.45; 95% CI 0.35-0.57 versus CSHR 0.56; 95% CI 0.44-0.70). Although based on a limited number of cases, the analysis further stratifying Gram-positive bacteraemia cases suggested that *S. aureus* and 'other Gram-positives' had a stronger association with ICU mortality than CNS (CSHR 1.35, 95% CI 0.63-2.85 and CSHR 1.39, 95% CI 0.92-2.09 vs. CSHR 1.00, 95% CI 0.74-1.37). In contrast, *S. aureus* and other Gram-positives did not seem to have a stronger effect on ICU discharge than CNS (*S. aureus* CSHR: 0.65, 95% CI 0.48-0.87; CNS CSHR: 0.53, 95% CI 0.45-0.63; other Gram-positives: 0.63, 95% CI 0.48-0.83).

Discussion

ICU acquired bacteraemia was associated with an increased ICU mortality risk (CSHR 1.29; 95% CI 1.02-1.63) and a decreased daily ICU discharge risk (CSHR 0.54; 95% CI 0.47-0.62), even after adjusting for potential time-varying confounding and the time-dependent nature of the exposure. Our results suggest that ICU mortality could be noticeably lowered (in our study from 20.3% to 18.6% by 60 days) by preventing ICU-acquired bacteraemia.

We applied various modelling strategies to our data that are applied in the literature. We illustrated that substantially different results can be obtained when conditioning on time-varying factors instead of using techniques like marginal structural models with IPW. Using this former modelling strategy bias may be introduced due to adjustment for factors that are

likely affected by bacteraemia itself and due to collider stratification bias.^{15,17} Although the estimates obtained using the analysis completely ignoring time-varying confounding were very similar to the results obtained using the marginal structural model with IPW, this should not be assumed to always be the case without testing.^{3,17} Both simulation studies and studies using real data, including a recent study assessing the effect of ICU-acquired enterococcal bacteraemia, showed that marginal structural models with inverse probability weighting are often necessary to adjust for time-dependent confounders that are affected by exposure.^{3,14,17,26,27} For example, the effect of enterococcal bacteraemia was overestimated using a conventional Cox model only adjusting for baseline confounders.³

Strengths and limitations

An important strength of this study is that it is one of the first studies assessing the effects of ICU-acquired bacteraemia while addressing simultaneously the time-varying nature of this type of exposure, potential time-varying confounding and competing risks. One study has been published that used similar methodology to estimate cumulative mortality incidence associated with, specifically, enterococcal bacteraemia.³ Unfortunately, in our study, a separate estimate for enterococci resulted in very wide confidence intervals prohibiting a meaningful comparison.

Time-varying confounders should not be modelled using conventional regression techniques that condition on time-varying factors that may be affected by exposure. Instead marginal structural models with IPW, such as applied in the current study, could be used. When extreme weights are generated, fitting marginal structural models via IPW is not reliable.²² In that regard, it is a pity that researchers often fail to report the distribution of the estimated weights including maximum and minimum values.^{3,25} The estimated weights in our study are not considered extreme weights.

However, despite marginal structural models with IPW being able to adequately adjust for time-varying confounding, these techniques remain vulnerable to unmeasured confounding. Deterioration prior to acquiring bacteraemia may have been insufficiently captured by measuring the daily APACHE II score, administration of antibiotics, mechanical ventilation, central lines and renal replacement therapy. In a study that focused on the effect of ICU-acquired enterococcal bacteraemia, using similar methodology, adjustment for time-varying sequential organ failure assessment (SOFA) score, prior antibiotic use and abdominal perforation or surgery resulted in more moderate effect estimates compared to a Cox model with adjustment for baseline confounders.³ Hence, in our study, the effect of ICU-acquired bacteraemia may have been overestimated.

Some of the samples classified as bacteraemia may have actually been contaminated blood samples. Particularly, blood cultures positive for CNS may be contaminated blood samples, instead of true infections.³ The stronger associations observed for ICU-acquired Gram-negative bacteraemia are therefore in line with expectations, although the difference between both groups could not be completely explained by the inclusion of CNS.

Due to data limitations in records from recent years, we necessarily had to restrict our analysis to the years 2002–2006. Since then, the number of Gram-negative bacteraemia cases

resistant to the most widely used antibiotics has increased.²⁸ Therefore, the current impact of ICU-acquired bacteraemia caused by Gram-negative bacteraemia may be even higher than the estimates in this study. Especially the impact on ICU discharge may have been underestimated, given the fact that a recent English study found that antibiotic resistance among *E. coli* increases length of stay, but did not seem to have a significant impact on in-hospital mortality.²⁹

In our study, even after adjusting for the timing of acquiring bacteraemia and time-varying confounding using IPW for marginal structural models, ICU-acquired bacteraemia was associated with a substantial increased daily risk of ICU mortality and decreased daily ICU discharge risk.

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Table I. Baseline patient characteristics and crude length of stay and mortality rates for admissions during which ICU-acquired bacteraemia developed vs. did not develop

	Admissions during which bacteraemia developed (n=671)	Admissions during which bacteraemia did not develop (n=2,488)
Male sex, n (%)	434 (64.7)	1483 (59.6)
Age, mean (SD)	61.8 (15.52)	60.8 (17.30)
APACHE II, mean (SD)	19.1 (6.42)	18.0 (6.45)
Admission type		
Medicine, n (%)	402 (59.9)	1521 (61.1)
Surgery, n (%)	269 (40.1)	967 (38.9)
ICU length of stay, median (Q1,Q3)	21 (13, 34)	6 (4, 9)
ICU mortality, n (%)	208 (31.0)	444 (17.8)

Abbreviations: ICU, intensive care unit; SD, standard deviation.

Table II. Association between ICU-acquired bacteraemia and ICU mortality and discharge.

	ICU mortality CSHR (95% CI)	ICU discharge CSHR (95% CI)
Adjustment for baseline variables only	1.28 (1.04-1.57)	0.51 (0.45-0.58)
Adjustment for baseline and time-varying variables using conventional Cox model	1.08 (0.88-1.32)	0.68 (0.60-0.77)
Adjustment for baseline and time-varying variables using marginal structural model with inverse probability weighting	1.29 (1.02-1.63)	0.52 (0.45-0.60)

Abbreviations: CI, confidence interval; CSHR, cause-specific hazard ratio; ICU, intensive care unit.

Figure 1. Observed intensive care unit (ICU) mortality vs expected ICU mortality without ICU-acquired bacteraemia. The solid line represents the observed ICU mortality in the patient cohort and the dashed line the expected mortality if all ICU-acquired bacteraemia in the same cohort would have been prevented.

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Appendix 1.

Example collider-stratification bias

Collider-stratification bias is introduced by conditioning on a collider, a variable that is a common effect of two or more variables in a causal pathway.¹ For example, consider the causal diagram presented in Figure A1. Suppose the value of the time-varying confounders at time t (C_t), e.g. a disease severity score like APACHE II or SOFA, is predicted by previous bacteraemia (Inf_{t-1}), but also predicts subsequent bacteraemia (Inf_t) and the risk of ICU death ($Death_t$). In that situation, C_t is a collider on the causal path from previous bacteraemia to ICU death through C_t ($Inf_{t-1} \rightarrow C_t \rightarrow Inf_t \rightarrow Death_t$). By conditioning on this collider (C_t), a spurious path will be opened from bacteraemia to ICU death, via the unmeasured common causes (U) of confounders and outcome ($Inf_t \rightarrow C_t \rightarrow U \rightarrow Death_t$), hence, inducing collider-stratification bias.³ In addition, conditioning on C_t will adjust away the (indirect) effect of previous bacteraemia (Inf_{t-1}) via later confounders (C_t), which are also intermediates, resulting in a biased estimate of the effect of bacteraemia on ICU death. While adjusting away the (indirect) effect of the exposure will attenuate the effect estimate, collider-stratification bias may even result in effect estimates in the opposite direction of the true effect.^{1,2,3}

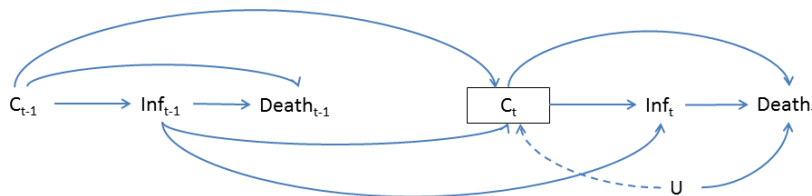


Figure A1. Directed acyclic graphs (DAGs) representing possible causal associations among time-varying potential confounders (C), bacteraemia (Inf), death and potentially unmeasured factors (U). t , current time; $t-1$ previous time.

References

1. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology*. 2003;14:300-6.
2. Whitcomb BW, Schisterman EF, Perkins NJ, Platt RW. Quantification of collider-stratification bias and the birth weight paradox. *Paediatr Perinat Epidemiol* 2009;23:394-402.
3. Ali MS, Groenwold RHH, Pestman WR, Belitser SV, Hoes AW, de Boer A, Klungel OH. Time-dependent propensity score and collider-stratification bias: an example of beta₂-agonist use and the risk of coronary heart disease. *Eur J Epidemiol* 2013;28:291-299.

Appendix 2

Model to create inverse probability weights:

Daily probabilities of acquiring bacteraemia in the ICU were estimated using a pooled logistic regression model (logistic regression with each day within a patient treated as a separate observation). The final model was obtained by first adding main effects to the model and sequentially removing those that were nonsignificant at the 20% level. Non-linear effects were included in the model for the weights by using restricted cubic splines quadratic terms. We allowed for interactions between type of admission and APACHE II score at admission. Interactions and smoothing terms were added if significant at the 5% level.

The following time-varying variables were included in the final model: the presence of central lines, mechanical ventilation, administration of antibiotics and the APACHE II score. Because time-varying variables measured on a given day may have been influenced by infection acquired on that day, only lagged values from the day before were included in the models. For the APACHE II score and antibiotic use we adjusted for lagged values 2 days before to acknowledge that the APACHE II score and antibiotic use within 24 hours before the onset of bacteremia are potentially surrogate markers for an infection that was incubating and hence may be affected by bacteremia on that day.

To stabilize the weights the following variables were included: age, age-squared, gender, APACHE II score at admission, mechanical ventilation at admission and antibiotic administration at admission. Non-linear effects of time were included by using restricted cubic splines with four knots.

The estimated inverse probability weights used in the marginal structural models had a median and mean of 0.99 and 1.01, an interquartile range and standard deviation of 0.14 and 0.31 (min 0.26, max 4.49).

For the analysis estimating the effect of Gram-negative bacteraemia, the weights obtained above were multiplied, from the time of acquiring bacteraemia onwards, by the stabilized inverse conditional probability that the bacteraemia involved Gram-negative bacteria, given the time-varying confounders on the previous day. These latter estimates were obtained using a logistic regression model. This model included the following time-varying variables: renal replacement therapy and the APACHE II score. For the APACHE II score we used lagged values from 2 days before, as done for the 'any bacteraemia' model. To stabilize the weights the 'presence of central lines at admission' was included.

The final estimated inverse probability weights used for this analysis had a median and mean of 0.99 and 1.01, an interquartile range and standard deviation of 0.13 and 0.31 (min 0.22, max 4.65).

Appendix 3

R code used to obtain cumulative incidence function for ICU mortality

The R code below was used to obtain the cumulative incidence function for mortality, by combining the results of the cause-specific hazards for ICU mortality and ICU discharge. This code adapts work by Therneau *et al.*¹ on calculating cumulative incidences based on cause-specific hazards, to the context of Marginal Structural Cause-specific Hazard Models.

```
library(survival)

# cause-specific model for ICU discharge
cfit1 <- coxph(Surv(fuptime1, fuptime2, ICU_discharge) ~
  bacteraemia + Age + Sex + max_apache_score_admission + ventilated_admission +
  number_sys_antibiotic_admission + cluster(id), data=data, weights=IPWweight)

# cause-specific model for ICU death
cfit2 <- coxph(Surv(fuptime1, fuptime2, ICU_death) ~
  bacteraemia + Age + Sex + max_apache_score_admission + central_lines_admission +
  cluster(id), data=data, weights=IPWweight)

# create a transition matrix
temp <- matrix(list(),3,3)
dimnames(temp) <- list(from=c("Alive","Discharge","Death"),
  to=c("Alive","Discharge","Death"))

# create new data based on old data with bacteraemia set to 0 for all patients
newdata <- data
newdata$bacteraemia <- 0

# get one line for each patient
newdata <- newdata[unique(newdata$id),]

# calculate the transition rates
a <- survfit(cfit1, newdata, std.err=FALSE)
b <- survfit(cfit2, newdata, std.err=FALSE)

# populate the transition matrix
temp[1,2] <- list(a)
temp[1,3] <- list(b)

# calculate the cumulative incidence function
csurv <- survfit(temp,p0=c(1,0,0))

# average over all patients to get marginal estimates for ICU mortality
x <- csurv$time[1:89]
d <- matrix(csurv$pstate[,3],ncol=89,byrow=T)
d3<-apply(d,2,mean)
```

```
# plot the data for the first 60 days
```

```
plot(stepfun(x,c(0,d3)),xlim=c(0,60),do.points=F, main="", xlab="Days in the ICU", ylab="Cumulative probability  
of ICU-mortality")
```

References:

1. Therneau T, Crowson C, Atkinson E. Multi-state models and competing risks. October 29, 2016.
<https://cran.r-project.org/web/packages/survival/vignettes/compete.pdf>. Accessed January 30, 2017.

Appendix 4

Table I. Association between ICU-acquired bacteraemia and ICU mortality estimated using marginal structural model with inverse probability weighting.

	CSHR (95% confidence interval) ^c
Bacteraemia ^a	1.29 (1.02-1.63)
Age (years)	1.01 (1.00-1.01)
Gender ^b	0.83 (0.71-0.98)
APACHE II score admission	1.08 (1.07-1.10)
Central lines admission (yes/no)	1.23 (1.01-1.50)

^a Bacteraemia was coded as a time-varying variable that was 1 from the day bacteraemia was acquired and onwards and 0 otherwise.

^b Gender was coded as a binary variable with male gender set to 1.

^c Adjusted for the following time-varying variables using inverse probability weighting: the presence of central lines, mechanical ventilation, administration of antibiotics and the APACHE II score.

Table II. Association between ICU-acquired bacteraemia and ICU mortality estimated using conventional Cox model adjusting for baseline and time-varying confounders.

	CSHR (95% confidence interval)
Bacteraemia ^a	1.08 (0.88-1.32)
Gender ^b	0.77 (0.66-0.91)
Mechanical ventilation admission (yes/no)	0.80 (0.63-1.00)
<i>Time-varying variables</i>	
Renal replacement therapy (yes/no)	1.66 (1.40-1.96)
APACHE II score	1.25 (1.18-1.33)
APACHE II score-squared	1.00 (1.00-1.00)
Central lines (yes/no)	1.49 (1.17-1.90)
Mechanical ventilation (yes/no)	1.83 (1.36-2.47)
Number of systemic antibiotics	0.95 (0.89-1.01)

^a Bacteraemia was coded as a time-varying variable that was 1 from the day bacteraemia was acquired and onwards and 0 otherwise.

^b Gender was coded as a binary variable with male gender set to 1.

Table III. Association between ICU-acquired bacteraemia and ICU mortality estimated using conventional Cox model adjusting for baseline confounders.

	CSHR (95% confidence interval)
Bacteraemia ^a	1.28 (1.04-1.57)
Age (years)	1.01 (1.00-1.01)
Gender ^b	0.79 (0.68-0.93)
APACHE II score admission	1.16 (1.09-1.23)
APACHE II score admission-squared	1.00 (1.00-1.00)
Central lines admission (yes/no)	1.18 (0.98-1.42)

^a Bacteraemia was coded as a time-varying variable that was 1 from the day bacteraemia was acquired and onwards and 0 otherwise.

^b Gender was coded as a binary variable with male gender set to 1.

Table IV. Association between ICU-acquired bacteraemia and ICU discharge estimated using marginal structural model with inverse probability weighting.

	CSHR (95% confidence interval) *
Bacteraemia ^a	0.52 (0.45-0.60)
Age (years)	1.00 (0.99-1.00)
Gender ^b	1.10 (1.01-1.20)
APACHE II score admission	0.95 (0.95-0.96)
Mechanical ventilation admission (yes/no)	0.71 (0.64-0.79)
Number of systemic antibiotics admission	0.91 (0.88-0.95)

^a Bacteraemia was coded as a time-varying variable that was 1 from the day bacteraemia was acquired and onwards and 0 otherwise.

^b Gender was coded as a binary variable with male gender set to 1.

^c Adjusted for the following time-varying variables using inverse probability weighting: the presence of central lines, mechanical ventilation, administration of antibiotics and the APACHE II score.

Table V. Association between ICU-acquired bacteraemia and ICU discharge estimated using conventional Cox model adjusting for baseline and time-varying confounders.

	CSHR (95% confidence interval)
Bacteraemia ^a	0.68 (0.60-0.77)
Gender ^b	1.08 (0.99-1.17)
Central lines admission	1.26 (1.14-1.40)
Mechanical ventilation admission (yes/no)	1.83 (1.63-2.05)
Renal replacement therapy admission (yes/no)	1.29 (1.09-1.52)
Number of systemic antibiotics admission	0.93 (0.89-0.97)
<i>Time-varying variables</i>	
Renal replacement therapy (yes/no)	0.51 (0.44-0.60)
APACHE II score	0.94 (0.93-0.94)
Central lines (yes/no)	0.71 (0.64-0.78)
Mechanical ventilation (yes/no)	0.18 (0.17-0.20)
Number of systemic antibiotics	0.85 (0.81-0.88)

^aBacteraemia was coded as a time-varying variable that was 1 from the day bacteraemia was acquired and onwards and 0 otherwise.

^bGender was coded as a binary variable with male gender set to 1.

Table VI. Association between ICU-acquired bacteraemia and ICU discharge estimated using conventional Cox model adjusting for baseline confounders.

	CSHR (95% confidence interval)
Bacteraemia ^a	0.51 (0.45-0.58)
Age (years)	1.00 (0.99-1.00)
Gender ^b	1.12 (1.03-1.21)
APACHE II score admission	0.95 (0.95-0.96)
Mechanical ventilation admission (yes/no)	0.69 (0.63-0.75)
Number of systemic antibiotics admission	0.91 (0.88-0.95)

^aBacteraemia was coded as a time-varying variable that was 1 from the day bacteraemia was acquired and onwards and 0 otherwise.

^bGender was coded as a binary variable with male gender set to 1.

